IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NATURAL ALTERNATIVES INTERNATIONAL, INC., *et al.*,	)	
Plaintiffs,	)	C.A. No. 09-626-GMS
v.	)	**JURY TRIAL DEMANDED**
VITAL PHARMACEUTICALS, INC., *et al.*	)	
Defendants.	)	
VITAL PHARMACEUTICALS, INC.,	)	
Counterclaim/Third-Party Plaintiff,	)	
v.	)	
NATURAL ALTERNATIVES INTERNATIONAL, INC., and COMPOUND SOLUTIONS, INC.,	)	
Counterclaim/Third-Party Defendant.	)	

PLAINTIFFS' ANSWERING BRIEF
IN SUPPORT OF CLAIM CONSTRUCTION

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Plaintiffs, Natural Alternatives International Inc., Roger Harris, Mark Dunnett, and Kenny Johannson (collectively "NAII"), respectfully submit this Memorandum in Response to Defendants' March 25, 2011 Claim Construction Brief. NAII seeks to properly construe the terms at issue in U.S. Patent Nos. 5,965,596 ("the '596 patent"), 6,172,098 ("the '098 patent") and 6,426,361 ("the '361 patent") (collectively "the patents-in-suit"). Vital Pharmaceuticals Inc. and DNP International Co., Inc. (collectively, "defendants") lack support for their positions in the intrinsic evidence and are forced to rely on unsupported extrinsic evidence. They also resort to statements taken out of context in an attempt to confuse the issues and broaden clearly disavowed claim scope. Additionally, defendants misconstrue the statute relating to dependent claims, ignore case law, the prosecution history and the plain meaning of the claims. Most importantly, they ignore common sense: the Examiner would not have permitted the claims to issue if they were construed as defendants request. For the reasons set forth below and in their Opening Brief (D.I. 76), Plaintiffs' claim construction should be adopted.

I. DEFENDANTS' CONSTRUCTION OF BETA-ALANINE AND L-HISTIDINE DISTORTS THE PLAIN LANGUAGE OF THE SPECIFICATION AND IGNORES THE PROSECUTION HISTORY.

If defendants are correct, the Examiner would have refused to issue the patent: after all, he had a prior art reference using dipeptides that would have invalidated the claims at issue as well as those in related applications. The Examiner, however, allowed the claims, based on the applicants' affirmative statement that their invention did not encompass the dipeptides disclosed in the prior art. Defendants twist and distort the plain language of the specification and ignore the prosecution history in an attempt to have the claims encompass prior art. The defendants assert that the applicants specifically defined β-alanine and L-histidine to include dipeptides, oligopeptides and polypeptides. (D.I. 77 at 5). To be clear, the applicants did not. The portion

of the specification that defendants point to merely discloses some of the various embodiments of the invention, not what the claims encompass. "Each of the beta-alanine or L-histidine **can be** in the form of the individual amino acids, **or** components of dipeptides, oligopeptides, or polypeptides." JX 3 at col. 2, ll. 42-45 (emphasis added). It is not defining β-alanine or L-histidine, but indicates potential sources. β-alanine and L-histidine were not defined to include dipeptides, oligopeptides, or polypeptides; rather, the applicants gave several options for embodiments that could supply the β-alanine of the invention.

Even if the Court concluded this is a definition, it is at most multiple definitions. As discussed in NAII's Opening Brief, when the specification provides multiple definitions for a term, the court should avoid those definitions upon which the Patent Office could not reasonably have relied when it issued the patent and that definitions of terms contained in the specification can be modified by statements made before the Patent Office during prosecution. (D.I. 76 at 7-8, citing *Genentech, Inc. v. Wellcome Found., Ltd.*, 29 F.3d 1555, 1563-64 (Fed. Cir. 1994); *Rheox, Inc. v. Entact, Inc.*, 276 F.3d 1319, 1327 (Fed. Cir. 2002); *Spectrum Int'l, Inc. v. Sterilite Corp.*, 164 F.3d 1372, 1379-80 (Fed. Cir. 1998)). Additionally, when the scope of claims has been narrowed "to obtain issuance over the prior art [the claims] cannot later be interpreted to cover that which was previously disclaimed during prosecution." *Elektra Instrument v. O.U.R. Scientific Int'l*, 214 F.3d 1302, 1308 (Fed. Cir. 2000) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 33 (1966)). As explained previously, the applicants affirmatively disclaimed that dipeptides such as carnosine were encompassed by the claims. JX 4 at JA73-74.

Defendants assert that where the inventors define a claim term in the specification, that definition governs and cites to *Phillips* to support this assertion. (D.I. 77 at 5). The *Phillips* court was discussing the circumstance where the specification gives a clear, unique meaning to a

term that is different than the meaning it would otherwise possess, not where—as here—the specification was describing embodiments clearly disclaimed in the prosecution history. *Phillips v. AWH Corp. et al.*, 415 F.3d 1303, 1316 (Fed. Cir. 2005). Most importantly, defendants ignore those parts of *Phillips* that discuss how the prosecution history is used to construe the claims and *Phillips'* reaffirmance of the importance of the prosecution history. *See, e.g., id.* at 1315 ("[t]he best source for understanding a technical term is the specification from which it arose, informed, as needed, by the prosecution history.").[1] The *Phillips* court did not state that the specification overrules the prosecution history; rather, the prosecution history must be consulted to determine if the claim was narrowed during prosecution despite what may be present in the specification.

Defendants also assert that the applicants used the terms β-alanine and L-histidine consistent with the alleged definition throughout the specification (D.I. 77 at 5), citing selected portions of the specification out of context as support and drawing incorrect conclusions from these passages. For example, the first citation, to the "Background of the Invention" section, describes dipeptides with residues of β-alanine and L-histidine, from which defendants draw the conclusion "this indicates that the terms 'beta-alanine' and 'histidine' encompass beta-alanine and histidine in the dipeptide form." (D.I. 77 at 5). This is absurd. That section of the specification is merely informing one of skill in the art that the individual amino acids, β-alanine and L-histidine, can be combined to form dipeptides that are present in muscle fibers of many animals, including humans. JX 3 at col. 2, ll. 1-12.

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[1] *See also id.* ("The words of patent claims have the meaning and scope with which they are used in the specification and the prosecution history."); *id.* at 1317 ("Like the specification, the prosecution history provides evidence of how the PTO and the inventor understood the patent."); *id.* ("the prosecution history can often inform the meaning of the claim language by demonstrating how the inventor understood the invention and whether the inventor limited the invention in the course of prosecution, making the claim scope narrower than it would otherwise be."); *id.* ("The purpose of consulting the prosecution history in construing a claim is to 'exclude any interpretation that was disclaimed during prosecution'") (citations omitted).

Defendants reference Example 2 of the specification and draw a similar conclusion. Specifically, the defendants point out: "In one session, 8 milliliters per kilogram body weight of broth containing approximately 40 milligrams per kilogram body weight of beta-alanine (*e.g.*, **in the form of anserine and carnosine**) was ingested." JX 3 at col. 10, ll. 64-67 (emphasis added). As scientists explaining their discovery, this is not surprising; however, from this defendants erroneously conclude that β-alanine encompasses dipeptides such as carnosine and anserine. (D.I. 77 at 6). The section merely discloses one of the embodiments that the inventors envisioned when they conceived of their invention. It also shows that the inventors did not use the terms β-alanine or L-histidine synonymously with carnosine, or anserine, because they understood them to be **different** compositions and specifically pointed out the difference.

Similarly, the defendants erroneously cite to Table 4 in the specification. Table 4 shows, however, that the inventors did not understand the term β-alanine to encompass dipeptides. Table 4 summarizes an experiment and sets forth 6 different treatments: 1 broth treatment, 1 carnosine treatment and 4 β-alanine treatments. JX 3 at col. 11, ll. 21-38. This demonstrates the inventors recognized various sources for β-alanine, but they did not consider β-alanine to encompass dipeptides, such as carnosine, because they particularly called out β-alanine as a separate treatment, not once, but four times.

The "definition" propounded by the defendants is not a definition, but a disclosure of the various embodiments of the invention: the citations set forth by the defendants support this position. Example 2 describes experiments in which subjects were given the individual amino acid β-alanine, broth, or carnosine. *See, e.g.*, JX 3 at col. 11, ll. 21-38. The other examples in the specification only use the individual amino acids, not dipeptides. Example 1 describes experiments in which horses were given the individual amino acids β-alanine and L-histidine.

See, e.g., JX 3 at col. 6, ll. 56-64. Examples 3 and 4 describe experiments where subjects were given the individual amino acid β-alanine. *See, e.g.*, JX 3 at col.11, ll. 63-67; col. 12, ll. 60-65. Arguably, the preferred embodiment of the inventors was the individual amino acids, β-alanine and L-histidine and Example 2 demonstrates that β-alanine can be used to supplement a normal diet. *See, e.g.*, JX 3 at col. 10, ll. 24-25. Additionally, Figure 8 demonstrates that the individual amino acid β-alanine produced an increase in plasma concentrations of β-alanine over the concentration found in the plasma of individuals "fed" chicken broth, which contains carnosine. The statement in the specification that "administration of carnosine equivalent to 20 milligrams per kilogram body weight of beta-alanine in one test subject resulted in an equivalent increase in the plasma beta-alanine concentration" (JX 3 at col. 11, ll. 47-52), merely discloses the inventors' hypothesis that the β-alanine residue in carnosine could be recycled by the body back into carnosine. This basic science experiment does not address what the claimed invention is.

The defendants also try to distort the plain language of the statute by asserting that claim 3 of the '361 patent narrows the scope of the composition of claim 1. (D.I. 77 at 7). The statute states "a claim in dependent form shall contain a reference to a claim previously set forth and then specify **a further limitation** of the subject matter claimed." 35 U.S.C. § 112, ¶ 4 (emphasis added). Claim 3 of the '361 patent uses the term "further comprises," of which the plain and ordinary meaning is "additionally contains." *See, e.g., Remediation Products Inc. v. Adventus Americas Inc. et al.*, No. 3:07cv153-RJC, 2009 WL 57456 at *1 (W.D.N.C. Jan. 7, 2009) ("The construction of the phrase 'further comprising' includes *additional* recited elements.") (emphasis added); *accord Monsanto Co. v. Syngenta Seeds, Inc.*, 503 F.3d 1352, 1357-58 (Fed. Cir. 2007). Claim 3 of the '361 patent, therefore, does not narrow the meaning of β-alanine, rather it adds an additional limitation required to be present in an infringing product. By statute, this limitation

cannot be present in the independent claim. 35 U.S.C. § 112, ¶ 4. If the claim said "wherein the beta alanine ***is*** a dipeptide, oligopeptide or a polypeptide" it might provide support for defendants' position. *But see*, *ICU Medical v. Alaris Medical Sys.*, 558 F.3d 1368 (Fed. Cir. 2009) (rejecting claim differentiation as an inimitable rule).[2] Here, however, the claim merely says the composition further adds additional material.

Later prosecution also supports this position. The applicants filed further patent applications that issued after the '361 patent, *e.g.*, U.S. Patent No. 7,825,084 ("the '084 patent"). (Declaration of William John McKeague ("McKeague Decl.") Ex. A). The '084 patent claims priority to, among other things, the patents-in-suit and, as such, is in the same family of patents where terms should be construed consistently.[3] *Microsoft Corp. v. Multi-Tech Systems, Inc.*, 357 F.3d 1340, 1350 (Fed. Cir. 2004) (holding that statements made during prosecution of related patents was relevant to claim construction of earlier issued patent because "[a]ny statement of the patentee in the prosecution of a related application as to the scope of the invention would be relevant to claim construction"). The Patent Examiner is the same Examiner as for the patents-in-suit. McKeague Decl. Ex. A; JX 1 at JA1; JX 2 at JA23; JX 3 at JA49. During prosecution of the '084 patent, the Examiner raised a nonstatutory obviousness-type double patenting rejection of the then pending claims over, *inter alia*, the '361 patent, stating that then pending claims 13-16—directed to a composition of a mixture of creatine and carnosine, anserine, or balenine—

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2 *Edwards Lifesciences v. Cook*, 582 F.3d 1322 (Fed. Cir. 2009) (rejecting claim differentiation to clarify construction); *Regents of Univ. Cal. v. Dakocytomation Cal.*, 517 F.3d 1364 (Fed. Cir. 2008) (accord); *Netcraft v. eBay*, 549 F.3d 1394 (Fed. Cir. 2008) (accord).

3 *NTP, Inc. v. Research in Motion, Ltd.*, 418 F.3d 1282, 1293 (Fed. Cir. 2005); *Omega Eng'g, Inc v. Raytek Corp.*, 334 F.3d 1314, 1333 (Fed. Cir. 2003); *Ormco Corp. v. Align Technology, Inc.*, 498 F.3d 1307, 1315-16 (Fed. Cir. 2007); *MBO Labs, Inc. v. Becton, Dickinson & Co.*, 474 F.3d 1323, 1327 (Fed. Cir. 2007).

were obvious in view of claims 1-4 of the '361 patent. McKeague Decl. Ex. B at 3. Responding, applicants stated:

> [i]nstant claims 13-16 do not embrace the compositions of claims 1-4 of the '361 patent, because the instant compositions do not recite or encompass compositions that include, *e.g.*, a mixture of creatine and anserine or balenine. Further, none of claims 1-4 of the '361 patent recites a composition that includes a mixture of creatine and anserine or balenine [dipeptides of beta-alanine],[4] nor do claims 1-4 of the '361 patent recite or suggest any modification that would result in the compositions of instant claims 13-16.

McKeague Decl. Ex. C at 24. The prosecution history specifically notes the Examiner reviewed the parent prosecution on at least two occasions before allowing the claims based on these arguments. McKeague Decl. Exs. D and E. This is yet further evidence that the applicants made a clear disavowal that the term beta-alanine encompassed dipeptides, such as carnosine and anserine, and the Examiner understood this and allowed the claims in the '084 patent to issue. *See also* JX 4 at JA73-74 (affirmative disclaimer of dipeptides in the patents-in-suit).

Defendants also allege that the statements made by the applicants during prosecution are not a clear disavowal of claim scope. (D.I. 77 at 9-10). To support this, defendants state that the applicants made contradictory statements in the Petition to Make Special filed during prosecution of the '596 patent. Again, the defendants misleadingly quote out of context and distort the plain meaning. The inventors describe the invention as relating to methods for increasing the anaerobic working capacity of muscle and other tissues. JX 4 at JA73. The inventors also state that the method "includes simultaneous accumulation of creatine and beta-alanylhistidine dipeptides, or beta-alanine and L-histidine analogues within a tissue in the body," and that "[t]he accumulation of these dipeptides and peptide analogues is related to the provision of beta-alanine to a subject." *Id.* The portion defendants rely upon states: "[t]he methods of the present

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[4] *See* JX 3 at col. 2, ll. 1-12 (indicating anserine and balenine are dipeptides containing the β-alanine residue).

invention include providing the dipeptides, peptides, or peptide analogues by any number of means including, for example, ingestion and injection." *Id.* It is clear that the dipeptides that this portion refers to are the beta-alanylhistidine dipeptides that **accumulate** within a tissue because β-alanine is ingested, and that the applicants used the term β-alanine separately from these dipeptides.

Also, as pointed out in NAII's Opening Brief, the applicants distinguished their invention over the prior art by disclaiming any claim scope where β-alanine or L-histidine would encompass these amino acids in the form of dipeptides found in the prior art, such as carnosine. (D.I. 76 at 10-11). This was a clear disavowal, despite defendants' arguments to the contrary. The applicants admitted that the prior art, Setra:

> describes compositions containing a carnosine dipeptide and uses of the composition in treating muscle fatigue and athletic performance. Carnosine is a dipeptide, namely β-alanyl-L-histidine. According to the Setra invention, other 'dipeptides containing histidine imidazole ring can be used' (page 2). Such 'other peptides' are defined as homocarnosine, anserine, homoanserine and ophidine.

JX 4 at JA73. Thus, Setra anticipates using dipeptides. Further, the applicants stated:

> **In contrast to the present invention**, the compositions and methods described in Setra's invention teaches dipeptides. In the present invention, β-alanine and/or L-histidine are administered to regulate hydronium ion concentrations. Setra does not teach, suggest or mention using monopeptides for the treatment of hydronium ions.

JX 4 at JA74 (emphasis added) How could the disavowal be more clear? Such a statement distinguishes the invention over the prior art and is a clear disavowal that the claims, which are directed to methods and compositions using β-alanine and/or L-histidine, encompass dipeptides such as carnosine. If the claimed invention did include dipeptides, how could the Examiner possibly issue the claims in view of Setra? *Genentech*, 29 F.3d at 1563-64 (rejecting constructions that the Examiner could not have relied upon).

Defendants also assert that statements made during the prosecution of the '361 patent to support new claims that correspond to issued claim 3 support their proposed construction. (D.I. 77 at 9). As stated above, claim 3 of the '361 patent adds a further limitation and does not narrow the scope of the term β-alanine in claim 1. As stated above, the applicants affirmatively stated that the claims of the '361 patent, specifically claims 1-4, did not encompass dipeptides such as carnosine or anserine and the Examiner agreed. McKeague Decl. Exs. C and D. The terms β-alanine and L-histidine, therefore, do not encompass dipeptides such as carnosine.

Defendants cite case law for the proposition that when the prosecution history is in conflict with the specification, then the specification shall govern. (D.I. 77 at 10). Their support is telling. The case law cited by the defendants deals with the situation where applicants try to ***enlarge*** the scope of the claims beyond what is disclosed in the specification not where—as here—the applicants **narrowed** the claim. *See, e.g.*, *Lydall Thermal/Acoustical, Inc. v. Federal-Mogul Corp.*, No. 2009-1135, 2009 WL 2893190 at *6 (Fed. Cir. Sept. 8, 2009) (nonprecedential) ("The patentee's efforts during the prosecution of the reissue patent to enlarge the claims beyond what the specification discloses also must fail."); *Telecordia Techs., Inc. v. Cisco Sys., Inc.*, 612 F.3d 1365, 1375 (Fed. Cir. 2010) (stating that the applicant made statements during prosecution enlarging the claim scope to contain "multiple data packets, [but] the specification does not disclose any mechanisms that would allow more than one packet per frame."). During prosecution of the patents-in-suit the applicants did exactly the opposite, they narrowed the scope of the claims, which is common and entirely permissible. In doing so, they disavowed any claim scope encompassing dipeptides such as carnosine. *See, e.g.*, *Genentech,* 29 F.3d at 1563-64; *Rheox,* 276 F.3d at 1327; *Spectrum Int'l*, 164 F.3d at 1379-80; *Phillips*, 415 F.3d at 1317-18; JX 4 at JA73-74.

Next, the defendants erroneously turn to extrinsic evidence, in the form of an "expert" declaration to try and encompass the prior art. "[C]onclusory, unsupported assertions by experts as to the definition of a claim term are not useful to a court . . . [especially when the construction] 'is clearly at odds with the claim construction mandated by the written description, and the prosecution history.'" *Phillips*, 415 F.3d at 1318 (citations omitted). This type of extrinsic evidence suffers from bias not present in the intrinsic evidence because it is generated specifically for the purpose of litigation and may not be subject to cross-examination. *Id.* Here, defendants offer the conclusory statement of Malcom Watford that one of skill in the art would have understood the terms β-alanine and L-histidine to encompass dipeptide, oligopeptides and polypeptides. (D.I. 77 at 8). Upon examination of his declaration, however, Dr. Watford does not cite to anything to support this conclusion. (D.I. 79 at ¶ 12). This is precisely the type of "conclusory, unsupported assertion" that should be ignored by the Court. *Phillips*, 415 F.3d at 1318.

The defendants also allege that scientific publications and abstracts published many years after the filing date and issuance of the patents-in-suit support their proposed construction. Again, this must fail. Extrinsic evidence is unlikely to provide reliable evidence of what the inventors meant **as of the filing date**. *Id.* at 1319. The extrinsic evidence discloses that a β-alanine residue can be found as a covalently linked fragment of dipeptides, such as carnosine and anserine. It does not provide any evidence as to how the inventors defined or intended the term β-alanine to be used in the patents-in-suit or the claims, particularly since they issued years before. Defendants are resorting to extrinsic evidence in a vain attempt to find something that supports their position. "In the course of litigation, each party will naturally choose the pieces of extrinsic evidence most favorable to its cause, leaving the court with the considerable task of

filtering the useful extrinsic evidence from the fluff." *Id.* at 1318. The Court should ignore the "fluff" cited by the defendants and rely on the intrinsic evidence, which clearly shows that the applicants intended that the terms β-alanine and L-histidine do not encompass dipeptides, such as carnosine. Thus, the Court should construe the terms β-alanine to mean "the individual amino acid, beta-alanine, or its salt, ester or amide" and L-histidine to mean "the individual amino acid, L-histidine, or its salt, ester, or amide."

II. DEFENDANTS' CONSTRUCTION OF DIETARY SUPPLEMENT IGNORES THE PLAIN LANGUAGE OF THE SPECIFICATION.

Dietary Supplements are intended to supplement the diet. If constituents are in the diet, there is no need for a supplement. Defendants ignore the overwhelming evidence supporting NAII's proposed construction, which is fully supported by the specification. Defendants are correct that the specification repeatedly describes dietary supplements as products added to the diet, but is wrong that the specification repeatedly describes supplements as conventional food stuffs. (D.I. 77 at 11). Defendants again point to Example 2 for the proposition that a dietary supplement is a conventional food. Defendants, however, ignore the repeated statements in the specification that a dietary supplement is *not* a conventional food stuff. *See, e.g.*, JX 3 at col. 11, ll. 21-38; col. 6, ll.56-64; col. 11, ll. 63-67; col. 12, ll. 60-65. For instance, Example 2 describes experiments in which subjects were given the individual amino acid β-alanine (in liquid form). *See, e.g.*, JX 3 at col. 11, ll. 21-38. The other examples disclosed use only the individual amino acids, not conventional food stuffs. Example 1 describes experiments in which horses were given the individual amino acids β-alanine and L-histidine in free base form (either powder or liquid). *See, e.g.*, JX 3 at col. 6, ll. 56-64. Examples 3 and 4 describe experiments in which subjects were given the individual amino acid β-alanine (in either powder, liquid or tablet form). *See, e.g.*, JX 3 at col.11, ll. 63-67; col. 12, ll. 60-65. There is overwhelming evidence to

support Plaintiffs' proposed construction that the dietary supplement must be in pill, capsule, tablet, powder or liquid form, which is not a conventional food.

Also, defendants ignore the numerous references in the specification that dietary supplements of the invention effectively increase the function of tissues when consumed. JX 3 at col. 1, ll. 18-30; col. 3, ll. 50-54; col. 3, ll. 60-65. For example, the specification states, "[n]atural food supplements are typically designed to compensate for reduced levels of nutrients in the modern human and animal diet. In particular, useful **supplements increase the function of tissues** when consumed. It can be particularly important to supplement the diets of particular classes of animals whose the normal diet may be deficient in nutrients available only from meat and animal produce (*e.g.*, human vegetarians and other animals consume an herbivorous diet)." JX 3 at col. 1, ll. 18-25 (emphasis added); *see also* col. 3, ll. 50-54; col. 3, ll. 60-65.

Additionally, defendants argue that there is no support in the specification for the proposition that a dietary supplement cannot be a conventional food stuff. This ignores the plain language of the specification. The specification expressly states that, "[t]he compositions and methods can contribute to correcting the loss of beta-alanine, L-histidine, or creatine due to degradation or leaching of these constituents during cooking or processing. The compositions and methods can also contribute to correcting the absence of these components from a vegetarian diet." JX 3, col. 3, ll. 54-59. In other words, the dietary supplements of the invention are not conventional food stuffs because the processing removes the β-alanine.

Also, the extrinsic evidence cited by the defendants states that diet means "food or drink regularly provided or consumed," and "dietary supplements" means "something that completes or makes an addition [to the diet]." (D.I. 77 at 11, citing Walter Declaration Ex. D.). The use of dictionary definitions, however, is littered with problems, most notably that "the patent applicant

did not create the dictionary to describe the invention." *Phillips*, 415 F.3d at 1321. The use of a dictionary definition risks changing the meaning of a term because it is construed out of context, *i.e.*, it does not consider the use of the term in the specification by the inventors. *Id.* When this dictionary definition proposed by the defendants is taken in the context of the specification, it is clear that dietary supplement is something that is added to the diet and is not a conventional food because conventional foods lack β-alanine and are already present in the diet. Accordingly, the Court should construe the term "dietary supplement" to mean "an addition to the normal diet in a pill, capsule, tablet, powder, or liquid form, which is not a conventional food, and effectively increases the function of tissues when consumed."

III. PLAINTIFFS' CONSTRUCTION OF ACTIVE DERIVATIVE IS SUPPORTED BY THE INTRINSIC EVIDENCE AND DOES NOT EXCLUDE THE PREFERRED EMBODIMENT.

Plaintiffs' construction of the term "active derivative" comports with the specification and the prosecution history. Defendants ignore the clear disavowal of claim scope in the prosecution history. Contrary to defendants' assertion, the limitation that active derivative does not include dipeptides, oligopeptides and polypeptides is not an "unstated limitation;" rather, it is clearly stated in the prosecution history. JX 4 at JA73-74; McKeague Decl. Ex. C. Defendants assert that the statement made during prosecution of the '596 patent only applies to those claims. (D.I. 77 at 14). To reach this conclusion, Defendants must ignore the case law and the prosecution history of the subsequent patents.

A claim term that appears in both the parent specification and continuation patent specifications should be construed identically in each. *See e.g., Omega Eng'g, Inc.*, 334 F.3d at 1333 (holding that disclaimers made during the prosecution of a patent will attach to even a CIP of the patent); *Ormco Corp.*, 498 F.3d at 1315-16 (holding that the claims were limited and did not include limitations found in the prior art that the applicants had disclaimed during

prosecution and that these statements applied to the claims in the other patents-in-suit); *Microsoft Corp.*, 357 F.3d at 1350 (holding that statements made during prosecution of related patents was relevant to claim construction of earlier issued patent because "[a]ny statement of the patentee in the prosecution of a related application as to the scope of the invention would be relevant to claim construction"). Thus the statements made in distinguishing the invention over the prior art limit the terms in the subsequent patents. This is especially true in this case where the Patent Examiner was the same in all the patents-in-suit and had the same prior art before him. JX 1 at JA1; JX 2 at JA23; JX 3 at JA49; JX 8; JX 10; JX 11. Additionally, as described above during prosecution of the '084 patent, in response to an Office Action rejecting the then pending claims in view of the claims of the '361 patent, the applicants stated that the claims of the '361 patent, **which contain the term active derivative**, do not encompass dipeptides such as carnosine and anserine and the Examiner agreed. McKeague Decl. Exs. C-E. The prosecution history, evidences a clear disavowal that **any** term in the patents-in-suit encompasses dipeptides such as carnosine or anserine, unless the claim term explicitly states dipeptide, anserine, or the like.

Defendants also assert that to exclude dipeptides, oligopeptides and polypeptides from the definition of an active derivative would exclude a preferred embodiment. (D.I. 77 at 14). Defendants' position is wrong. While a "claim interpretation that excludes a preferred embodiment from the scope of the claim is rarely, if ever, correct," (*On-Line Techs., v. Bodenseewerk Perkin Elmer GmbH*, 386 F.3d 1133, 1138 (Fed. Cir. 2004)), defendants ignore the case law that holds when there is highly persuasive evidence, a construction that excludes a preferred embodiment is permissible. Some of the preferred embodiments may be excluded from the scope of the claims because "[t]he prosecution history limits the interpretation of claim terms so as to exclude any interpretation that was disclaimed during prosecution.") *Rheox*, 276

F.3d at 1327 (citations omitted); *see also Elektra Instrument*, 214 F.3d at 1308 (holding that the construction that excluded a preferred embodiment was correct because "in light of the prosecution history and the unambiguous language . . . we conclude that this is the rare case in which such an interpretation is compelled").

Dipeptides, oligopeptides and polypeptides, are not the preferred embodiments. As stated previously, the preferred embodiments are the individual amino acids. Defendants again run to Example 2 in which a dipeptide of β-alanine and L-histidine is used, but ignore all the other uses of individual amino acids. While Example 2 describes experiments in which subjects were given the individual amino acid β-alanine, broth, or carnosine (JX 3 at col. 11, ll. 21-38), the other examples in the specification only use the individual amino acids, not dipeptides. Example 1 describes experiments in which horses were given the individual amino acids β-alanine and L-histidine. *See, e.g.*, JX 3 at col. 6, ll. 56-64. Examples 3 and 4 describe experiments in which subjects were given the individual amino acid β-alanine. *See, e.g.*, JX 3 at col.11, ll. 63-67; col. 12, ll. 60-65. Additionally, the results presented in Figure 8 demonstrate that the individual amino acid β-alanine produced an increase in plasma concentrations of β-alanine over the concentration found in the plasma of individuals "fed" a dipeptide containing broth. Moreover, the term "preferred embodiment" is not used in the specification to identify any particular embodiment. To the extent there was a preferred embodiment, given the extensive use of the individual amino acids, β-alanine and L-histidine, and the better results with these individual amino acids, the individual amino acids are the preferred embodiment, not dipeptides, oligopeptides and polypeptides. A construction that excludes dipeptides, oligopeptides and polypeptides is correct under the law and the facts. The Court need only ask how the Examiner, armed with the Setra dipeptide prior art, could issue claims directed to the dipeptide. Finally, as

explained in Plaintiffs' Opening Brief, active derivative is a chemical that can be made into β-alanine, not something like a dipeptide that must be broken into simple components and then used to build up β-alanine. Accordingly, the Court should construe the term active derivative to mean "a compound derived from, or a precursor of, the substance that performs in the same or similar way in the body as the substance, or which is processed into the substance and placed into the body, and excludes dipeptides, oligopeptides and polypeptides."

IV. DEFENDANTS OVERSIMPLIFY THE "PROVIDING AN AMOUNT" STEP OF THE METHOD CLAIMS, IGNORING THE INTRINSIC RECORD AND COMMON SENSE.

Defendants try and oversimplify the construction by ignoring the intrinsic record and basic principles of science. They also introduce ambiguity with the use of "directly or indirectly," not found in the specification, lacking any objective meaning to one of ordinary skill in the art and requiring further construction by this Court. Additionally, defendants assert that NAII's additions to the claim language are unsupported and do not clarify the meaning of the claim term to one of skill in the art. This is wrong.

Plaintiffs have set forth in their Opening Brief the support for their proposed construction of this term and explained why, due to basic principles of science that this construction is necessary. (D.I. 76 at 16-19). For example, the plaintiffs explained that the dipeptides in the muscle are synthesized from the precursor amino acids and that in a typically fed state, the concentration of β-alanine is much lower than L-histidine. JX 3 at col. 5, ll. 11-29. Plaintiffs explain that the carnosine synthase enzyme has a greater affinity for L-histidine than for β-alanine. *Id.* Thus, in a typically fed state the concentration of β-alanine is much lower than L-histidine and is not high enough to increase dipeptide synthesis in a human tissue. The term in dispute has the phrase "effective to increase beta-alanylhistidine dipeptide synthesis in a human

tissue." *See, e.g.*, JX 1 at claim 1. It is clear, therefore, that an amount of β-alanine, or L-histidine, "effective to increase beta-alanylhistidine dipeptide synthesis in a human tissue," must be higher than that which is found in a typically fed state. Plaintiffs' inclusion of this phrase in their proposed construction is supported by the intrinsic evidence. Additionally, this phrase is based on sound scientific principles due to the nature of the dipeptide synthesis in muscle that is disclosed in the specification. JX 3 at col. 5, ll. 11-29. One of ordinary skill in the art would readily understand that such a phrase is necessary for the construction of this term. Defendants' expert did not mention this issue in his declaration. The Court, therefore, should construe the term "providing an amount of [beta-alanine or L-histidine] to blood or blood plasma effective to increase beta-alanylhistidine dipeptide synthesis in a human tissue" to mean "supplying to a human an amount of [beta-alanine or L-histidine] by ingestion and therefore, causing an increase in [beta-alanine or L-histidine] in blood or blood plasma above normal concentrations found in a typical fed state, and thereby increasing the synthesis of beta-alanylhistidine dipeptide in the tissue."

V. DEFENDANTS' ATTEMPT TO CONFUSE THE ISSUE SURROUNDING INCREASING INSULIN IS WITHOUT MERIT.

Defendants' attempt to confuse the issue surrounding the term "increasing a concentration of insulin in the blood or blood plasma," and introduces ambiguity. Their proposed construction uses the phrase "directly or indirectly," which as discussed above, is not found in the specification and has no objective meaning to one of ordinary skill in the art. Defendants are correct that there is no restriction on how insulin levels are to be increased. Plaintiffs' construction clarifies this issue.

Defendants assert that Plaintiffs' proposed construction cherry-picks some, but not all of the examples in the specification and improperly imports these into the claim. (D.I. 77 at 20).

This is not the case. Plaintiffs properly clarify that the increasing step can include the direct injection or ingestion of insulin or agents that stimulate the production of insulin. Plaintiffs did not include carbohydrates in this as one of ordinary skill in the art would know that a carbohydrate is an agent that stimulates the production of insulin.[5] Plaintiffs' proposed construction also does not improperly import limitations from the specification into the claim, it defines the outer limits of the claim term. *See, e.g.*, *Phillips*, 415 F.3d at 1323. Improperly importing a limitation would be the case if the proposed construction was restricted to injection or infusion of insulin only as Defendants suggest. It is not. Plaintiffs' construction encompasses the full breadth of examples disclosed in the specification and so the specification is intended to be coexistent with the scope of this term. *Id.*

Furthermore, defendants erroneously assert that the phrase "agents that stimulate the production of insulin" adds more terms that likely need construction. (D.I. 77 at 20). Whether an agent stimulates the production of insulin is a question of fact, not claim interpretation. Nothing further needs to be construed in this phrase. Defendants' attempts to confuse the issue should be rejected and the Court, therefore, should construe the term "increasing a concentration of insulin in the blood or blood plasma" to mean "the concentration of insulin in the blood or blood plasma is increased by ingesting or infusing insulin, or agents that stimulate the production of insulin."

VI. DEFENDANTS' CONSTRUCTION OF UNIT DOSAGE FORM IS NOT FOUND IN THE INTRINSIC RECORD AND IS UNWORKABLE.

Defendants' proposed construction of unit dosage form is not found in the intrinsic record and it fully relies on extrinsic evidence As discussed above, the use of extrinsic evidence is limited. *Phillips*, 415 F.3d at 1321. The plain language of the claims and specification supports

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[5] Including carbohydrates, therefore, would be duplicative.

Plaintiffs' proposed construction. Defendants point to dependent claims 7 and 8 of the '361 patent (D.I. 77 at 15), but, these claims support Plaintiffs' position. The use of the term "one dose" in these dependent claims, shows that the applicants intended that the doses could be given in multiple parts throughout the day. Further, defendants do not address the issue of the size of the doses, which Plaintiffs have demonstrated in their Opening Brief would be impractical to contain in a single unit for human consumption. (D.I. 76 at 19). Defendants' proposed construction based on extrinsic evidence is unworkable and wrong. The Court, therefore, should construe the term "unit dosage form" to mean "doses of a certain serving size that can be taken all at once, or in multiple parts throughout the day."

VII. ANY AMBIGUITIES IN CONSTRUING CLAIM TERMS SHOULD BE RESOLVED TO PRESERVE THE VALIDITY OF THE CLAIM.

Any ambiguity surrounding the construction of any particular claim term, should be resolved by preserving the validity of the claim. The maxim that claims should be construed to preserve their validity is limited "to cases in which 'the court concludes, after applying all the available tools of claim construction, that the claim is still ambiguous.'" *Phillips*, 415 F.3d at 1327 (citations omitted). This maxim is based on the inference that the PTO would not have issued an invalid claim, "and that the ambiguity in the claim language should therefore be resolved in a manner that would preserve the patent's validity." *Id.*

This particularly applies to the terms "beta-alanine," "L-histidine" and "active derivative." Plaintiffs have explained in detail how those terms were limited by statements made during prosecution. Defendants argue that these clear disavowals of claim scope do not limit the terms as Plaintiffs suggest. If the Court finds the claim to still be ambiguous as to the presence of dipeptides, oligopeptides and polypeptides within the scope of these claim terms, it should resolve this issue by preserving the patent's validity. *Id.* at 1327.

Plaintiffs have explained that the applicants disclaimed any claim scope encompassing dipeptides such as carnosine during prosecution of the '596 patent. JX 4 at JA73-74. Further, the same prior art over which the claims in the '596 patent were distinguished was disclosed to the same Examiner during prosecution of the '098 and '361 patents. JX 8; JX 10; JX 11. The same Examiner allowed claims in a subsequent application (the '084 patent) following the applicants clear disavowal that the claims of the '596, '098 and '361 patents encompassed dipeptides such as carnosine or anserine. McKeague Decl. Exs. C-E. It is clear from all this that the Examiner recognized that a claim interpretation that encompasses dipeptides such as carnosine or anserine would have rendered the claims invalid and that in issuing the patents understood that the proper construction of the terms would necessarily exclude such a construction. *Phillips*, 415 F.3d at 1328. Any finding to the contrary ignores the extensive proceedings before the PTO and assumes that the PTO and specifically the Examiner did not perform the functions of his job according to the statute. A construction of the terms "beta-alanine," "L-histidine" and "active derivative," that excludes dipeptides such as carnosine or anserine is the only reasonable definition upon which the PTO could have relied when it issued the patents. *Id.* at 1327-28; *Genentech,* 29 F.3d at 1563-64. Accordingly, the Court should construe the terms as set forth in Plaintiffs' proposed constructions so as to not render claims of the patents-in-suit invalid.

CONCLUSION

For the aforementioned reasons, Plaintiffs respectfully request this Court to adopt their proposed claim construction.

Respectfully submitted,

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

CERTIFICATE OF SERVICE

I, David E. Moore, hereby certify that on April 12, 2011, the attached document was electronically filed with the Clerk of the Court using CM/ECF which will send notification to the registered attorney(s) of record that the document has been filed and is available for viewing and downloading.

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